Primary cutaneous anaplastic large cell lymphoma with angioinvasive features and cytotoxic phenotype: a rare lymphoma variant within the spectrum of CD30+ lymphoproliferative disorders

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Abstract: BACKGROUND: Primary cutaneous anaplastic large cell lymphoma (PCALCL) presents with solitary or grouped exophytic tumors and cohesive infiltrates of large CD30+ T cells. OBJECTIVE: To report an angioinvasive variant of PCALCL. METHODS: Retrospective analysis of clinicopathological features of this variant. RESULTS: The group consisted of six patients (median age 46 years) with a solitary flat necrotic lesion preferentially located on the upper extremity. Histologically, there were angiocentric and angiodestructive infiltrates of medium-sized to large pleomorphic and anaplastic cells co-expressing CD30 and CD8. Five patients were treated with surgical excision and one patient with radiotherapy. A relapse was observed in one patient with spontaneous regression of the lesions suggesting a link to the recently described angioinvasive lymphomatoid papulosis (type E). All patients were alive without evidence of disease after a median follow-up of 31 months (range 15-96), indicating an excellent prognosis. CONCLUSIONS: The angioinvasive variant of PCALCL is rare but distinctive and prone to misinterpretation as aggressive lymphoma due to its histological features.

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Primary Cutaneous Anaplastic Large Cell Lymphoma with Angioinvasive Features and Cytotoxic Phenotype: A Rare Lymphoma Variant within the Spectrum of CD30+ Lymphoproliferative Disorders

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Key Words
Cutaneous lymphoma · Anaplastic large cell lymphoma · Cytotoxic lymphomas · Angiocentric · CD30 · Lymphomatoid papulosis

Abstract
Background: Primary cutaneous anaplastic large cell lymphoma (PCALCL) presents with solitary or grouped exophytic tumors and cohesive infiltrates of large CD30+ T cells. ***Objective:*** To report an angioinvasive variant of PCALCL. ***Methods:*** Retrospective analysis of clinicopathological features of this variant. ***Results:*** The group consisted of six patients (median age 46 years) with a solitary flat necrotic lesion preferentially located on the upper extremity. Histologically, there were angiocentric and angiodestructive infiltrates of medium-sized to large pleomorphic and anaplastic cells coexpressing CD30 and CD8. Five patients were treated with surgical excision and one patient with radiotherapy. A relapse was observed in one patient with spontaneous regression of the lesions suggesting a link to the recently described angioinvasive lymphomatoid papulosis (type E). All patients were alive without evidence of disease after a median follow-up of 31 months (range 15–96), indicating an excellent prognosis. ***Conclusions:*** The angioinvasive variant of PCALCL is rare but distinctive and prone to misinterpretation as aggressive lymphoma due to its histological features.

Introduction

The spectrum of primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPD) comprises anaplastic large cell lymphoma (ALCL) and lymphomatoid papulosis (LyP) [1–9]. Five LyP types (A, B, C, D, E) have been identified in recent years, with some differences in the histopathological (and also clinical) appearances [10–13]. Irrespective of its histopathological pattern, LyP is clinically characterized by a variable number of self-healing papulonodular lesions, with the typical waxing and waning course, whereby individual lesions undergo spontaneous regression within a few weeks, sometimes accompanied by ulceration on top of the lesions and occasionally leaving behind varioliform scars [14–16].

LyP type E, also known as angioinvasive LyP, typically shows fewer lesions in comparison to other LyP types and characteristically manifests as eschar-like ulcers that often

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exceed the size of the pre-existing papules or nodules [12]. Angiocentric and angiodestructive infiltrates of CD30+ and mostly CD8+ lymphoid cells accompanied by necrotic areas are the typical histopathological features of this LyP variant. While working on the series of angioinvasive LyP, we observed 5 patients who displayed very similar if not identical morphological features, but presented with a solitary large cutaneous lesion without spontaneous regression of the lesion [12]. Thus these cases were classified as primary cutaneous ALCL (PCALCL) and were therefore excluded from the series of LyP. Available follow-up demonstrated that in all but one case the lesion remained solitary and there were no recurrences at other sites, in contrast to what was observed in patients with LyP type E. The goal of this paper is to present this rare variant of PCALCL with marked angiocentric and angiodestructive features and a CD30+CD8+ phenotype and to further demonstrate that LyP and PCALCL form a clinicopathological spectrum.

Subjects and Methods

The subjects of this report are 6 patients with a similar clinicopathological presentation, including occurrence of a large solitary cutaneous lesion as well as angiocentric and angiodestructive infiltrate of large atypical cells co-expressing CD30 and CD8. Of these, there were 2 newly identified patients and 4 of the 5 individuals who were originally excluded from the series of angioinvasive LyP [12].

Light Microscopy

Tissues were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and eosin-stained sections with a thickness of 4 μm were prepared. The following features were assessed: ulceration of the epidermis, epidermal hyperplasia, vacuolar alteration in the basal layer, prominent edema in the papillary dermis, perivascular or diffuse pattern of the infiltrates, infiltration and destruction of vessel walls, intraluminal thrombi, size (small, medium, large) and morphology (pleomorphic, anaplastic) of lymphoid cells, presence of eosinophils and neutrophils, extravasated erythrocytes, extension of the infiltrate into the subcutis, perineural or intraneural invasion and adnexal involvement.

Immunohistochemical Studies

Immunohistochemical studies were performed on formalin-fixed paraffin-embedded tissue using the following antibodies: CD2 (1:50; Novocastra/Leica-Microsystems, Heerbrugg, Switzerland), CD3 (1:75; Dako, Glostrup, Denmark), CD4 (1:2; Novocastra/Leica-Microsystems), CD5 (1:2; 4C7; Dako), CD7 (1:25; Dako), CD8 (1:400; Dako), CD20 (1:600; Dako), CD30 (1:75; Novocastra/Leica-Microsystems), CD56 (RTU; Novocastra/Leica-Microsystems), TIA (1:50; Immunotech, Marseille, France), T cell receptor (TCR)-βF1 (8A3; 1:50; Thermo Scientific, Fremont, Calif., USA), TCR-γ/δ (γ3.20; 1:100; Thermo Scientific) and CD246 (1:50; ALK-1; Dako). Appropriate positive controls were included. The number of antibodies used varied among individual cases depending on the available tissue. The results were assigned to one of the following four categories: immunoreaction in all of the affected vessels and in a majority of the interstitial (extramural) infiltrate (+); immunoreaction in a majority of the affected vessels and in a majority of the interstitial infiltrate (+/–); immunoreaction in a minority of the affected vessels and in a minority of the interstitial infiltrate (–/+); no immunoreaction in any of the affected vessels or in the interstitial infiltrate (–).

Molecular Biology

Five cases were studied for rearrangement of TCR-γ genes as described elsewhere [17]. In brief, the TCR clonality studies were performed using three multiplex polymerase chain reactions with different primers from the variable region in each reaction (reaction 1: Vg1 to 8; reaction 2: Vg9; reaction 3: Vg10, 11 and 12) and the same Cy-5-labeled primers from the conserved region (JGP1/2, JG1/2 and JGP). Additionally, in situ hybridization for EBV-encoded small RNA was performed (RTU; Novocastra/Leica-Microsystems) in 4 cases.

Results

Clinical Presentation

There were 4 female and 2 male patients, with age at diagnosis ranging from 27 to 70 years (mean 47, median 46). The lesions preferentially involved the upper extremity (4 cases, 67%), while the head and neck area and lower limbs were affected in the remaining 2 cases (table 1). At initial presentation, the lesions were solitary tumors ranging in size from 1 to 5 cm in largest diameter with ulceration mentioned clinically in half of the cases (fig. 1a). The lesions exceeded 2 cm in all but one case – the case with a 1-cm crusted lesion (case 6) which due to short history likely represented incipient disease (fig. 1b). After diagnosis, 5 patients underwent staging investigations to exclude extracutaneous disease, with negative results (in 1 patient pleomorphic adenoma of the parotid gland was found on work-up). Five patients were treated with excision only, whereas in the remaining case radiotherapy was administered. Follow-up ranged from 15 to 96 months (mean 39.5, median 31 months). None of the patients had any evidence of disease at the last check-up. Only 1 patient (case 5) experienced a relapse of disease with several grouped nodules occurring at the site of the original tumor 1 year after surgery. The lesions spontaneously regressed, but 2 years later several nodules developed, again regressing spontaneously.

Histopathological Features

In all cases, there was an angiocentric/angiodestructive infiltrate in the dermis with destruction of several small to medium-sized vessels that often showed fibrin deposits in their walls, intraluminal thrombi and perivas-

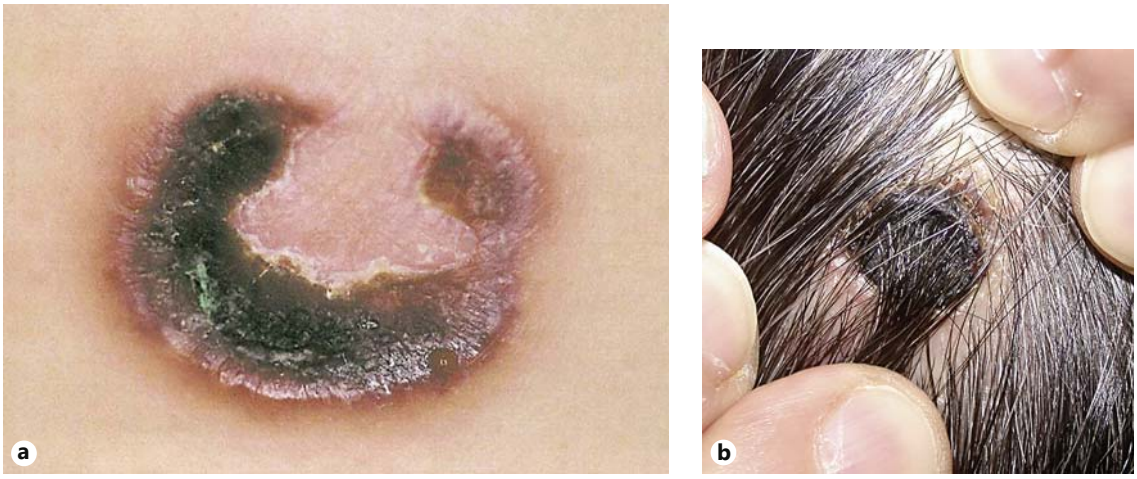

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Fig. 1. Clinical presentation of angiocentric ALCL: solitary ulcerated lesions covered by black eschar-like crust. A 5 × 4 cm tumor in case 5 (**a**) and a 1-cm scalp lesion in case 6 (**b**).

Table 1. Angioinvasive PCALCL: clinical features and follow-up of the patients

Case	Sex	Age	Clinical presentation	Staging/treatment	Follow-up
1	F	50	solitary ulcerated tumor on the forearm developing during 3 weeks from, reportedly, closely grouped, confluent pustules and papules; leishmaniasis? sporotrichosis?	not available/ radiotherapy	NED, 20 months
2	F	46	solitary tumor on the lower leg	negative/ excision	NED, 16 months
3	F	46	solitary tumor on the neck; keratoacanthoma?	negative/ excision	NED, 96 months
4	F	70	3.5-cm ulcerated tumor on the dorsal hand	negative/ excision	NED, 42 months
5	M	27	rapidly growing (over 2 weeks) solitary 5 × 4-cm tumor with central necrosis on the arm	negative/ excision	local relapse as several nodules 1 year later, with spontaneous regression; second identical relapse 2 years later, then NED at 48 months
6	M	42	recent solitary 1-cm plaque on the occipital area	negative/ excision	NED, 15 months

Case 1: history of laryngeal carcinoma. Case 4: pleomorphic adenoma of the right parotid gland found on staging investigations. NED = No evidence of disease.

cular debris (fig. 2). Around intact or partly destructed vessels, the neoplastic cells often formed dense cuffs, infiltrating the vessels wall. The cells were pleomorphic or anaplastic, medium-sized to large, some with conspicuous nucleoli. The infiltrate was either diffuse or perivascular, but the in latter case the 'perivascular' pattern rather resulted from conspicuous perivascular lymphoid cuffs in viable areas alternating with areas of dermal necrosis. Extension of the infiltrate into the subcutis was seen in half of the cases. Apart from atypical lymphocytes, numerous eosinophils and extravasated erythrocytes were a feature in a majority of cases (table 2).

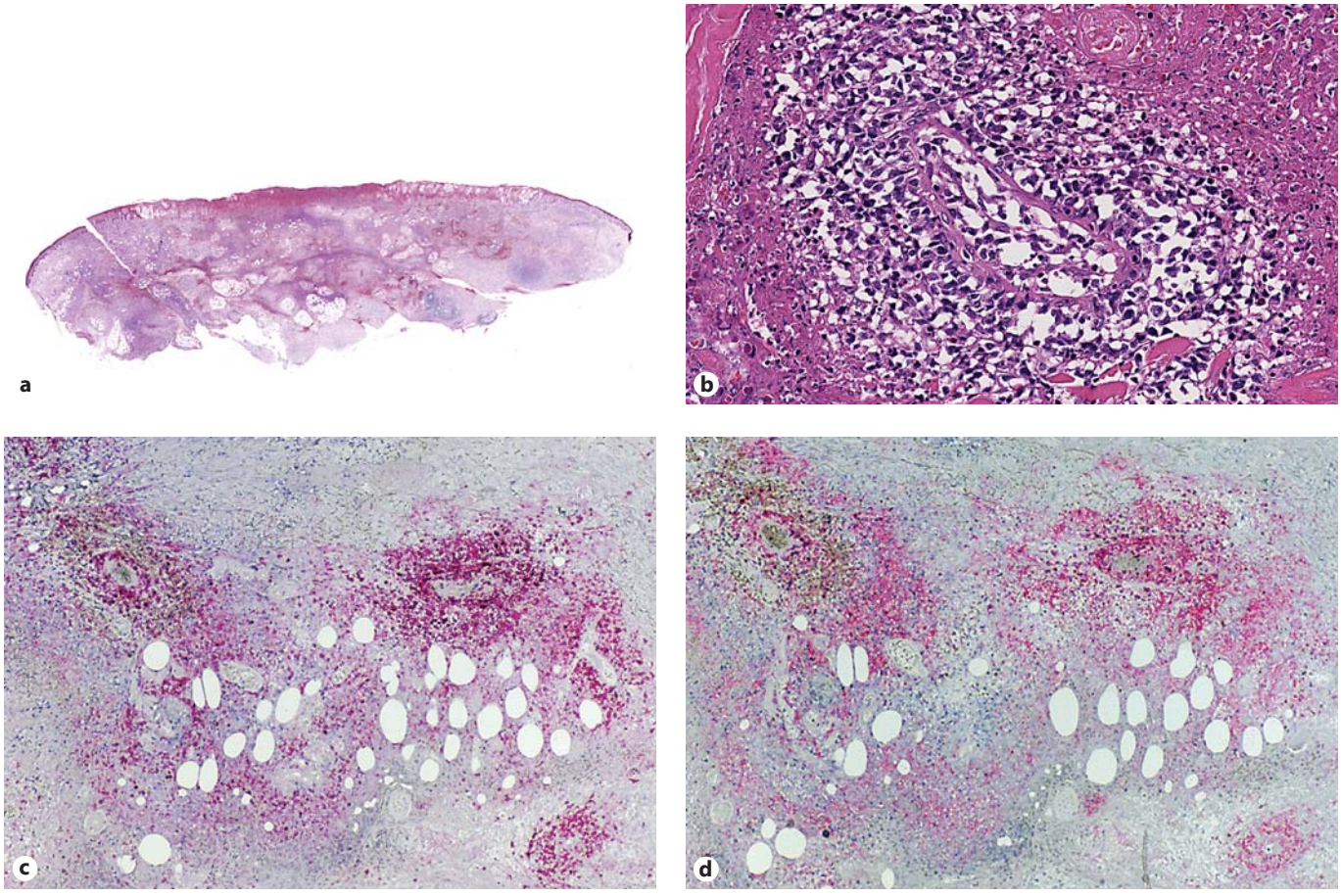

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Fig. 2. A dense non-epidermotropic infiltrate with angiocentric growth and involvement of several vessels in the dermis and subcutis and areas of dermal necrosis (**a**). Close-up view of pleomorphic cells infiltrating the vessel wall (**b**) co-expressing CD30 (**c**) and CD8 (**d**).

Immunohistochemical Findings

In all cases the neoplastic cells co-expressed CD30 and CD8. The results of immunostaining for the rest of the markers are summarized in table 3.

Molecular Biological Findings

Monoclonal TCR-γ gene rearrangement was found in 3 of the 5 cases studied. The remaining cases (cases 1 and 4) revealed no clonal T cell population. In none of the four investigated specimens was EBER detected.

Discussion

Occasional cases of PCALCL with angioinvasive infiltrates or cytotoxic phenotype have been reported in the literature, but this lymphoma variant (combining both

Table 2. Angioinvasive PCALCL: histopathological features

Ulceration of the epidermis	4/6
Epidermal hyperplasia	1/6
Vacuolar alteration in the basal layer	1/6
Prominent edema in the papillary dermis	0/6
Predominantly perivascular infiltrate	3/6
Predominantly diffuse infiltrate	2/6
Infiltration and destruction of vessel walls	6/6
Thrombi in the infiltrated vessels	4/6
Erythrocyte extravasation	4/6
Conspicuous eosinophils	4/6
Conspicuous neutrophils	1/6
Subcutis involvement	3/6
Perineural or intraneural invasion	0/6
Adnexal involvement	4/6

Table 3. Angioinvasive PCALCL: immunohistochemical features

Case	CD2	CD3	CD4	CD5	CD7	CD8	CD30	ALK	CD56	TIA	Gran	TCR-γ	βF1	EBER
1	+	+/–	+	+	–/+	+	+	–	–	–	ND	–	+	ND
2	+	–/+	+	+	–	+	+	ND	–	+	ND	ND	ND	–
3	+	+	+/–	+	–/+	+	+	–	–	+/–	ND	–	ND	–
4	+	+	+/–	+	+/–	+	+	–	–	+	+	–	+	–
5	+	+	+	+	–/+	+/–	+	–	–	–	ND	–	+	ND
6	+	+	–/+	+	+/–	+	+	–	–	–/+	ND	ND	+	–

Gran = Granzyme B; ND = not done.

features) has rarely been studied systematically [18, 19]. Plaza et al. [20] have recently reported 9 cases of CD30+ ALCL involving the skin with expression of CD8, including a single case of systemic ALCL secondarily involving the skin. None of the cases showed angiocentric/angiodestructive features. The only vascular involvement was represented by a striking intravascular localization of neoplastic cells seen in one case accompanied by significant extravascular infiltration by neoplastic cells. Parenthetically, apart from ALCL, the authors studied 12 cases of CD30+CD8+ LyP and noted angiocentricity of the infiltrate in half of them. Angiocentricity in LyP with or without cytotoxic phenotype has occasionally been reported [21–26]. In a large series of PCALCL, Massone et al. [18] identified angiodestruction in 10 of 66 specimens (15%) from 47 patients. Although no immunophenotype was provided, the authors commented that in their experience and that of others, cases of ALCL with angiodestruction often show cytotoxic phenotype. In the paper of Kummer et al. [27], who specifically studied the expression of cytotoxic molecules in cutaneous CD30+ LPD, no vascular abnormalities (angiocentric infiltrates) were however mentioned. In our series, expression of a cytotoxic phenotype was found in 4 out of the 6 cases.

In the present series, we investigated 6 cases of this entity which greatly resembles histopathologically angioinvasive LyP type E [12]. In fact, on the histopathological grounds alone these two conditions cannot be distinguished. Decisive is the clinical information (including history of the disease), but given that in some cases of angioinvasive LyP there may be a solitary lesion at initial presentation (or at a given time point), the discrimination between this ALCL variant and LyP type E can sometimes be achieved only during the follow-up of the patients. All our cases of LyP type E demonstrated in the course of the disease the typical course with occurrence of new lesions and regression of other lesions. Usually, the lesions in LyP type E persisted for 3–6 weeks before undergoing spontaneous regression. The first relapse usually occurred within 1 year, but in one case it took as long as 4 years after initial presentation, emphasizing the fact that in such rare cases one needs a long follow-up to classify the case as PCALCL or angioinvasive LyP [12]. Moreover, it cannot be entirely excluded that angiocentric PCALCL may precede angiocentric LyP in those patients.

This further reiterates the concept that LyP and PCALCL comprise a clinicopathological spectrum. A stereotypical example of LyP is characterized by multiple small (<2 cm) self-regressing lesions, with the typical waxing and waning course, whereas the classic presentation of PCALCL is that of a solitary large (usually >2 cm) lesion persisting longer (at least 3–4 weeks). In some cases of CD30+ LPD, patients present with few lesions and/or nodules measuring near 2 cm and such cases showing features of PCALCL are sometimes referred to as borderline [28]. A further demonstration of the clinicopathological continuum are rare cases where ALCL is followed by LyP or concomitant occurrence of large solitary lesions as typical for PCALCL and of small recurrent lesions as typical for LyP in the same patient [29]. In this respect, case 5 in the current series may also be regarded as a borderline case, as the patient first presented with a solitary 4 × 5 cm lesion, but experienced local recurrence with smaller nodules.

Given the angiodestructive pattern of the infiltrate, the differential diagnosis of this PCALCL variant, apart from LyP type E, also includes extranodal T/NK cell lymphoma, nasal type, cutaneous γ/δ-positive T cell lymphoma, adult T cell leukemia/lymphoma and EBV-associated hydroa vacciniforme-like lymphoma. The distinction from these aggressive lymphomas can in most cases be easily achieved by immunhistochemistry, as discussed else-

where [12]. Systemic CD30+ ALCL involving the skin is also a differential diagnostic consideration, as rare cases may manifest angiocentric/angiodestructive pattern in the skin [30]. Occasional cases of pityriasis lichenoides et varioliformis acuta (PLEVA) that show exuberant CD30+CD8+ lymphocytes and signs of vasculitis are easily distinguished from this ALCL variant clinically (multiple small erythematous macules quickly evolving into necrotic papules) and, besides, CD30+CD8+ cells in PLEVA are small lymphocytes showing no involvement of deeply located blood vessels [31]. Lastly, exceptional cases of cutaneous aggressive epidermotropic cytotoxic CD8+ T cell lymphoma can display an angiocentric pattern but lack expression of CD30 and show prominent epidermotropism of small lymphocytes [32].

In conclusion, we present a rare variant of ALCL characterized by an angiocentric/angiodestructive pattern and cytotoxic phenotype. The significance of recognition of this type lies in its obligate separation from aggressive lymphomas typified by an angioinvasive pattern, including nodal ALCL secondarily involving the skin. It shows phenotypic and histopathological overlap with LyP type E on the other hand, which further corroborates the concept of a clinicopathological spectrum of CD30+ LPD of the skin.

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Disclosure Statement

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